Pimecrolimus Cream 1%: A Potential New Treatment for Chronic Hand Dermatitis

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A multicenter, randomized, vehicle-controlled, 3-week study was conducted in patients with chronic hand dermatitis (HD) of various etiologies and locations to identify subgroups particularly responsive to twice-daily application of pimecrolimus cream 1% with overnight occlusion. A total of 294 patients were randomized to the study. By the final visit on day 22, there was a trend toward greater clearance in patients who received pimecrolimus than in those treated with vehicle cream. An analysis of treatment success by various stratification factors was performed, and it was found that palmar involvement had notable impact on response (P=.033). Patients in the pimecrolimus group continued to improve throughout the study; however, in the vehicle group, improvement plateaued after 15 days. Pimecrolimus was well tolerated, with a low rate of application-site reactions such as burning. Pimecrolimus cream 1%, when used twice daily with overnight occlusion, may be of benefit in the management of chronic HD.

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Hand dermatitis (HD) is among the most common of all occupational diseases, with an estimated prevalence of 5% in men and 10% in women.[1] Individuals in some occupations are affected at especially high rates. For example, almost 1 of every 3 nurses has been reported to have some form of HD.[1]

The signs and symptoms of HD include erythema, scaling, erosion, fissures, and pruritus. Together, these conditions can interfere with job performance and have a profound effect on quality of life.[2] Although repeated irritant exposure is important to the development of HD, its etiology often is complex, with multiple and overlapping factors contributing to disease risk. Patients with HD often have coexisting atopy.[3,4]

After HD enters the chronic phase, it becomes difficult to treat. Therapeutic options are limited by their effectiveness, convenience, or potential for adverse effects.[5] Affected individuals are advised to avoid chemical and mechanical irritants,[6] but in

Table 1.

Baseline Demographics

	Pimecrolimus Cream 1% (n=151)	Vehicle Cream (n=143)	Total (N=294)
Sex, no. (%)			
Men	57 (37.7)	61 (42.7)	118 (40.1)
Women	94 (62.3)	82 (57.3)	176 (59.9)
Race, no. (%)			
White	124 (82.1)	122 (85.3)	246 (83.7)
Nonwhite	27 (17.9)	21 (14.7)	48 (16.3)
Age, y			
Mean	44.8	44.3	44.6
Range	18–86	18–85	18–86

many cases, this is difficult or impractical. Although emollients provide symptomatic relief, they do little to alleviate the underlying inflammation. Topical corticosteroids, which are of value in treating other inflammatory skin diseases, can be effective in chronic HD,[7] but this class of drugs can have local adverse effects, especially cutaneous atrophy.[8,9] Protective creams or foams may be useful as preventive agents and can reduce the need for topical corticosteroids; however, they can pose compliance problems because they are not always convenient to use.[10]

Pimecrolimus is a nonsteroidal inhibitor of inflammatory cytokine release that was developed specifically for the treatment of inflammatory skin diseases.[11] In a previous 6-week, single-center pilot study, pimecrolimus cream 1% was found to ameliorate the signs and symptoms of chronic irritant HD.[12] Based on those results, a multicenter, randomized, vehicle-controlled, 3-week trial of pimecrolimus cream 1% in patients with chronic HD was initiated.

Methods

Study Design—The study was a double-blind, multicenter, vehicle-controlled trial of pimecrolimus cream 1% in adults with mild to moderate chronic HD. Patients were randomized to receive pimecrolimus cream 1% or corresponding vehicle cream twice daily for up to 3 weeks. Study drug treatment continued until complete clearance of chronic HD or completion of 3 weeks of treatment. The institutional review board at each center approved the protocol, and written informed consent was obtained from each patient.

Study Population—Patients admitted to the study were men or women volunteers 18 years or older who gave informed consent and had a 6-week or longer history of chronic HD. A baseline investigator's global assessment (IGA) score of mild to moderate disease, with at least mild scaling and mild erythema of the more severely affected hand, was required for enrollment.

Exclusion criteria included pregnancy; concurrent disease or treatments that could interfere with study evaluations; hypersensitivity to study drug ingredients; severe vesiculobullous dermatitis of the hands; contact urticaria; latex allergy; bullous disorders; hand-foot-and-mouth disease; mosaic warts; history of malignant disease or current premalignant skin conditions of the hands; and concurrent flaring of atopic dermatitis, psoriasis, or other concurrent skin disease of the hands requiring therapy. Also excluded were patients who had used systemic steroids within the previous month and patients who had used systemic antibiotics for infections of the hands or topical therapy for the hands within 7 days before screening. Patients with

Table 2.

Baseline Disease Characteristics*

	Pimecrolimus Cream 1%, No. (%) (n=151)†	Vehicle Cream, No. (%) (n=143)
IGA score distribution (target hand)		
Almost clear	1 (0.7)	0 (0)
Mild disease	49 (32.5)	37 (25.9)
Moderate disease	97 (64.2)	99 (69.2)
Severe disease	4 (2.6)	7 (4.9)
Suspected etiology		
ICD	62 (41.6)	55 (38.5)
Endo	46 (30.9)	48 (33.6)
ICD+endo	20 (13.4)	12 (8.4)
ICD+ACD	16 (10.7)	16 (11.2)
ACD	2 (1.3)	7 (4.9)
ACD+endo	1 (0.7)	3 (2.1)
ICD+ACD+endo	2 (1.3)	2 (1.4)

*IGA indicates investigator's global assessment score; ICD, irritant contact dermatitis; endo, endogenous disease (atopic dermatitis or dyshidrosis); and ACD, allergic contact dermatitis.
†Suspected etiology data were missing for 2 patients.

the following diseases, limited to the hands only, were eligible for inclusion: dyshidrosis, atopic dermatitis, and irritant or allergic contact dermatitis.

Treatments—Pimecrolimus cream 1% or corresponding vehicle cream was applied as a thin film twice daily to affected areas of the hands. The evening application was followed by occlusion for at least 6 hours using vinyl gloves. Barrier creams or emollients without α-hydroxy acids, urea, or vitamins A or E were permitted if applied to the hands more than one hour before or after study drug application. Hand washing (until 3 hours after study drug application) and irritants were to be avoided.

Visit Schedule and Evaluations—A baseline visit was followed by telephone contact on day 4 to obtain subjective assessment of pruritus and overall assessment of treatment effect. Visits to the clinical centers were scheduled for all patients on days 8 and 15, with a final visit on day 22. Laboratory tests were performed at baseline and end of study.

The target hand was defined as the more severely affected hand or the dominant hand if both were affected equally. Dorsal and palmar surfaces of each hand were evaluated together. The primary efficacy variable, IGA, was assessed using a 5-point scale defined by morphologic signs: scores ranged from 0 (clear) to 4 (severe). The target hand required baseline scores of 2 (mild) or 3 (moderate) for patient inclusion and a score of 0 (clear) or 1 (almost clear) to be considered a treatment success.

Statistical Methods—The intent-to-treat (ITT) and safety populations consisted of all randomized patients who received study medication, and the per-protocol population included all patients from the ITT population who did not violate the protocol in ways that would affect efficacy evaluations. Primary analysis was performed on the ITT population, with the per-protocol population investigated for sensitivity. Missing results were imputed

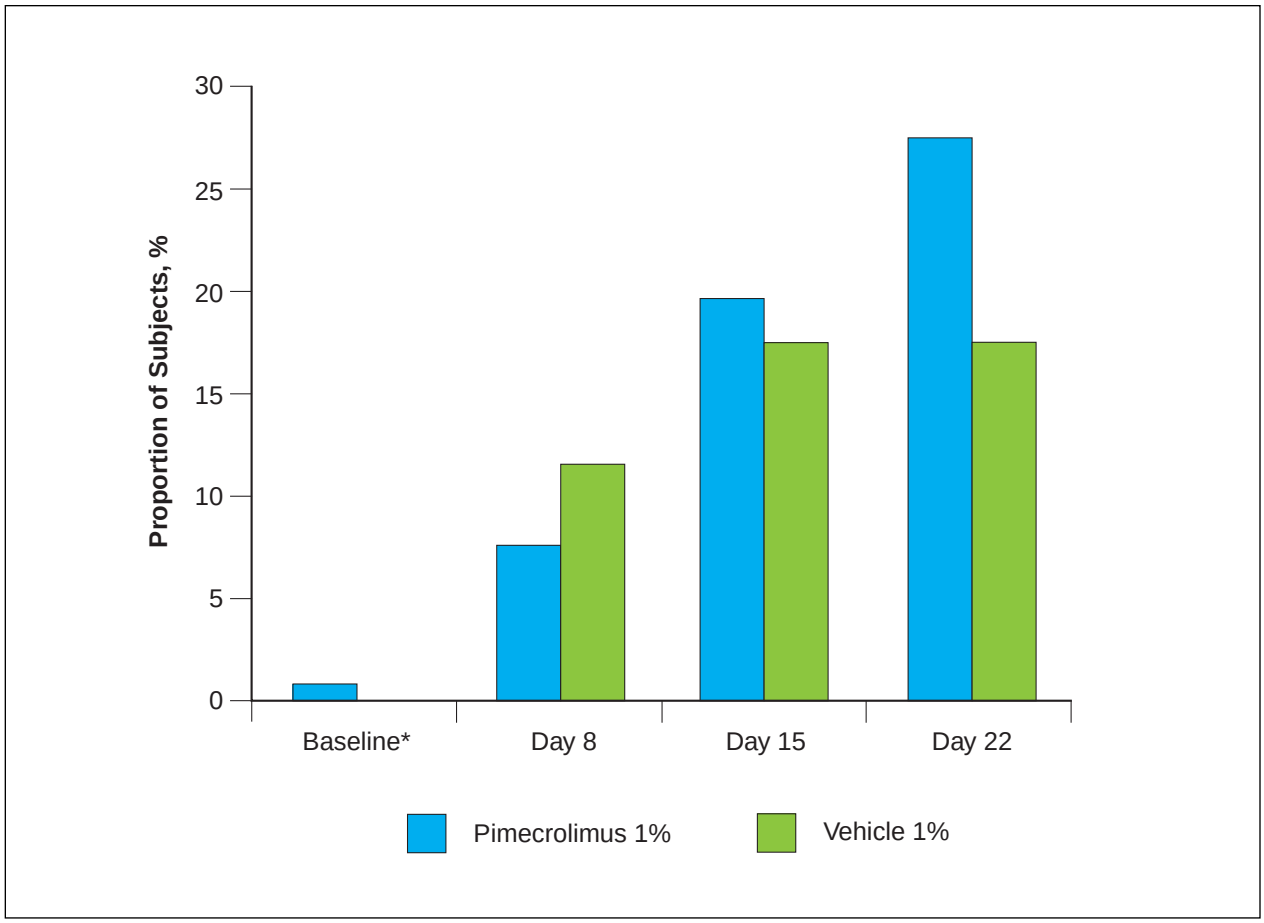

Figure 1. Treatment successes (defined as "clear" or "almost clear" of chronic hand dermatitis [investigator's global assessment score=0 or 1]) by visit. Asterisk indicates subject inclusion at baseline was an investigator's global assessment score of 2 (mild) or 3 (moderate).

using the last observation carried forward. The IGA was dichotomized into treatment success (0–1) or failure (2–4). The primary analyses of the dichotomized IGA scores at the end of the study were summarized by treatment group and visit using a Cochran-Mantel-Haenszel test stratified by center.

Results

A total of 294 patients with chronic HD were randomized to the study; 151 were assigned to the pimecrolimus cream 1% group and 143 to the vehicle cream group. There were no significant or clinically relevant differences between treatment groups in key demographic or baseline disease characteristics (Table 1). Disease severity at baseline was assessed using the IGA. The distribution of the IGA scores of the target hand at baseline was similar for the pimecrolimus cream 1% and vehicle groups (Table 2). The most common suspected disease determined at baseline was irritant contact dermatitis in both treatment groups, followed by endogenous disease. Of the mixed etiologies, irritant contact dermatitis concurrent with either endogenous disease or allergic contact dermatitis were the most frequent combinations. Disease patterns included palmar surface involvement (76.8%), dorsal involvement (53.0%), and dermatitis on the lateral surfaces of the fingers (72.2%).

Efficacy was measured by the proportion of treatment successes within each group at the final visit on day 22. A treatment success was defined as a determination of "clear" or "almost clear" (IGA=0 or 1) at postbaseline assessments. Assessments were made on the target hand, though both hands were treated. By days 15 and 22, a greater proportion of patients in the pimecrolimus cream 1% group were rated as treatment successes than in the vehicle group (Figure 1). The benefit of pimecrolimus cream 1% relative to the vehicle cream

Table 3.

Treatment Success (Defined as "Clear" or "Almost Clear" of Chronic Hand Dermatitis [IGA=0 or 1]) in Selected Groups*

	Pimecrolimus Cream 1%		Vehicle Cream		
	Baseline, n	Treatment Successes at Day 22, No. (%)	Baseline, n	Treatment Successes at Day 22, No. (%)	*P* value
Baseline hand dermatitis type†‡					.052
Irritant	100	26 (26.0)	85	13 (15.3)	
Allergic	21	3 (14.3)	28	3 (10.7)	
Endogenous	69	21 (30.4)	65	15 (23.1)	
Not assigned	2	0	0	0	
Palmar involvement§					.033
Present	116	27 (23.3)	98	17 (17.3)	
Absent	35	15 (42.9)	45	9 (20.0)	

*IGA indicates investigator's global assessment score.
†At baseline, patients were assessed as having one or a combination of hand dermatitis types.
‡Cochran-Mantel-Haenszel test stratified by baseline chronic hand dermatitis type.
§Cochran-Mantel-Haenszel test stratified by palmar involvement.

showed a trend by day 22 (P=.068). The proportion of treatment successes in vehicle-treated patients plateaued, with no further increase observed after day 15.

An analysis of treatment success was performed using various stratification factors to identify groups highly responsive to treatment (Table 3). Treatment with pimecrolimus cream 1% exhibited a significant advantage compared with the vehicle cream when outcomes were stratified by the absence/presence of palmar involvement (P=.033). The analysis revealed that treatment success with pimecrolimus was sensitive to baseline-suspected etiology, though this did not attain statistical significance (P=.052).

Photographic evidence of treatment success with pimecrolimus cream 1% applied to the palmar and dorsal aspects of the hands is shown in Figures 2 and 3, respectively. In both cases, the patients were ranked as having moderate disease at entry. They were "clear" or "almost clear" of disease signs after 22 days of treatment with pimecrolimus.

Discontinuations from the study occurred at similar rates in the pimecrolimus and vehicle groups (7.3% and 7.7%, respectively). Discontinuations specifically due to adverse events also occurred at similar rates in both groups (2.0% and 2.1%, respectively). None of the patients in the pimecrolimus-treated group left the study because of "unsatisfactory therapeutic effect" compared with 3 (2.1%) patients in the vehicle-treated group. There appeared to be no appreciable differences in the rates of occurrence of common adverse events in the pimecrolimus-treated and vehicle-treated groups. Application-site burning or unspecified application-site reactions were reported infrequently and occurred at a lower rate in the pimecrolimus group (0.7%) than in the vehicle group (2.1%).

Comment

Patients with chronic HD without palmar involvement responded better to treatment than those with palmar involvement. It is possible that a

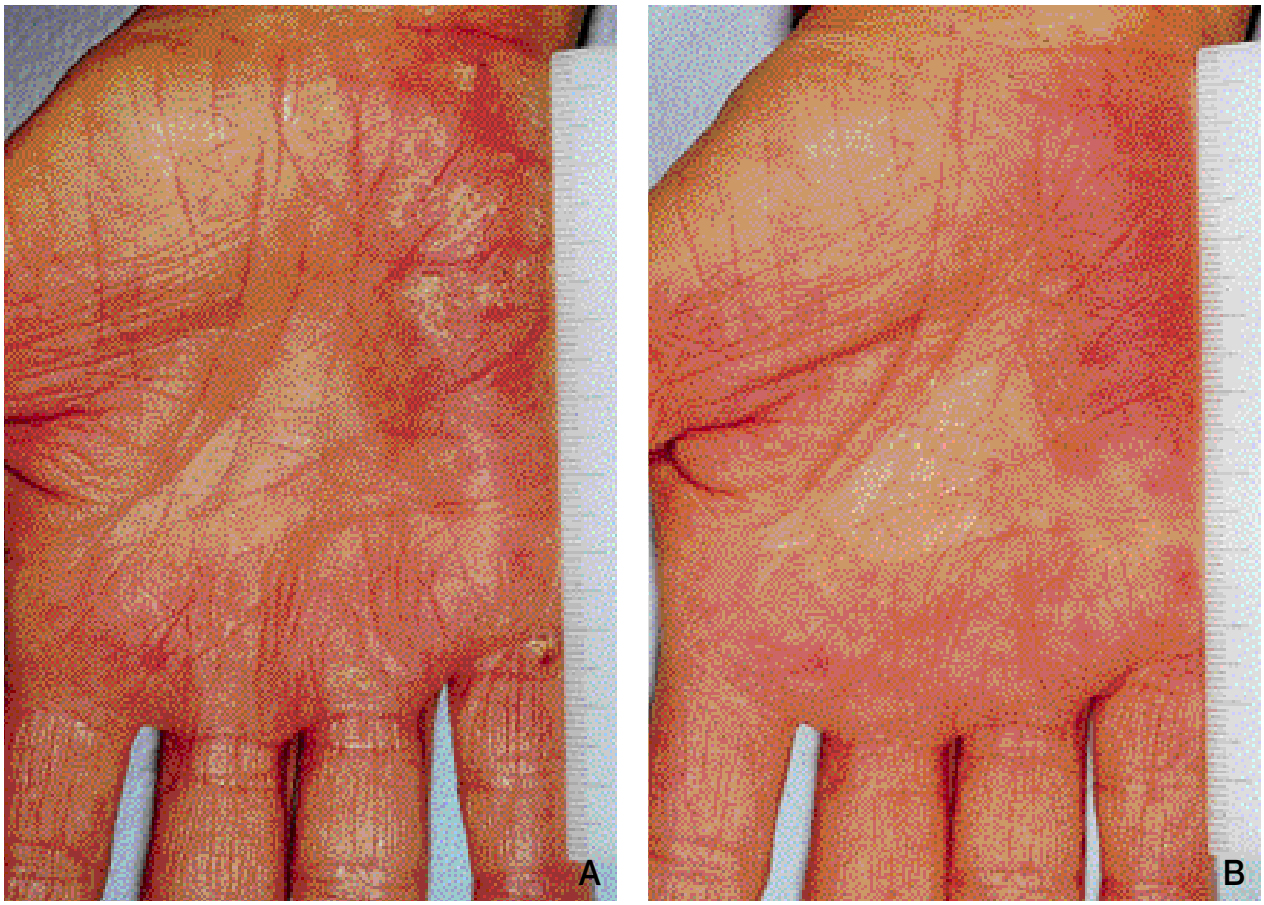

Figure 2. Chronic hand dermatitis before (A) and after (B) treatment with pimecrolimus cream 1% (palmar aspect). White woman (aged 69 years) who was rated with moderate (investigator's global assessment score=3) chronic hand dermatitis at baseline. Her condition was clear (investigator's global assessment score=0) on day 22.

significant treatment response to pimecrolimus in the other diagnostic groups would have been detected in longer-term studies because much of the response to vehicle occurred early and had plateaued by day 15, whereas the efficacy of pimecrolimus continued to increase (Figure 1). The vehicle, composed of cream, appears to have contributed to the treatment effect of pimecrolimus cream 1%, which is understandable because hydration, emollients, and barrier protection are used as a treatment for chronic HD.

In this multicenter, randomized, 3-week study, the proportion of patients with chronic HD who attained treatment success (IGA scores corresponding to "clear" or "almost clear") was greater in the pimecrolimus-treated group than in the vehicle-treated group; the result showed a trend but did not reach statistical significance. A search of the MEDLINE database failed to identify any large-scale controlled trials published during the past 10 years that evaluated drug treatment for chronic HD of various and mixed causes. Although there is a large body of literature concerning HD, much of it has focused on epidemiology and the identification of irritants and risk factors. Chronic HD is often a job-related disease, usually associated with exposure to wetness and exposure to mechanical or chemical irritants. Contact dermatitis, usually of the hands, is the most commonly reported of all occupational diseases in many countries.[13]

In the present study, chronic irritant exposure was the etiology most heavily represented, followed by endogenous disease, which included atopic and dyshidrotic dermatitis but excluded psoriasis, as determined by the clinical investigators. There were more women than men in the study, which is consistent with the relative prevalence of chronic HD reported in the sexes.[1]

Although topical corticosteroids are effective in treating inflammation, they can produce dermal atrophy[8] and cause allergic contact dermatitis.[9] Therefore, a topical nonsteroid would represent a

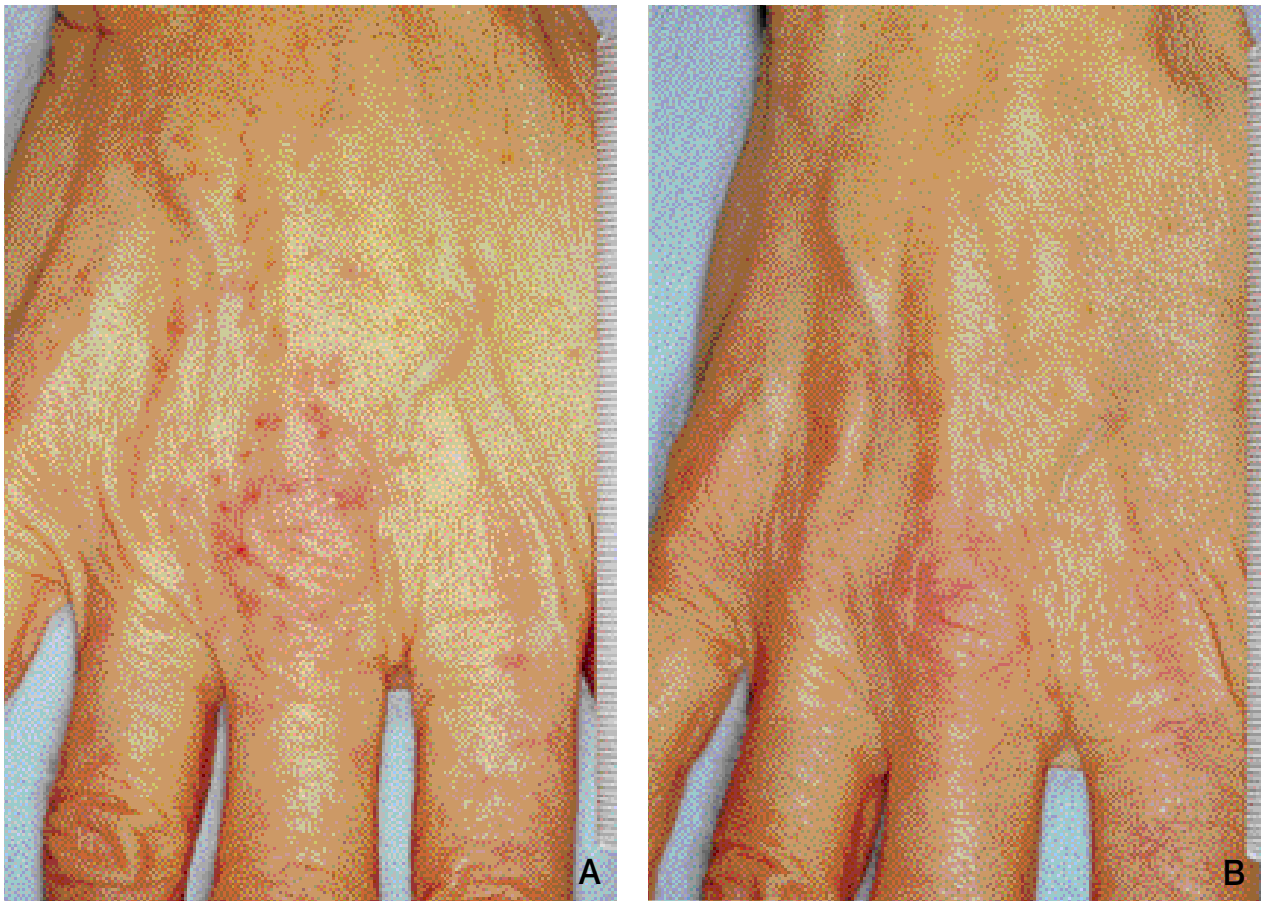

Figure 3. Chronic hand dermatitis before (A) and after (B) treatment with pimecrolimus cream 1% (dorsal aspect). White woman (aged 72 years) who was rated with moderate (investigator's global assessment score=3) chronic hand dermatitis at baseline. Her condition was almost clear (investigator's global assessment score=1) on day 22.

welcome addition to the limited treatment options available for chronic HD. Pimecrolimus is not a steroid, and preclinical and clinical studies have confirmed that pimecrolimus does not cause skin atrophy when topically applied in cream form.[14,15] Furthermore, pimecrolimus cream 1% selectively inhibits skin inflammation while having relatively low systemic immunosuppressant activity.[14]

In this study, pimecrolimus cream 1% was well tolerated. The cream formulation of the drug had a very low rate of local adverse effects such as burning, which is consistent with previous findings in patients with atopic dermatitis.[16] As previously demonstrated in a study of infants with extensive atopic dermatitis, the drug is not absorbed significantly after topical applications.[17] In this 3-week study of patients with moderate to severe chronic HD who used pimecrolimus cream 1% twice daily with overnight occlusion following the evening application, concentrations of pimecrolimus measured in blood were consistently low; in almost three quarters of the patients, blood concentrations were below the level of quantitation (0.1 ng/mL).[18] In conclusion, twice-daily applications of pimecrolimus cream 1% with overnight occlusion for 3 weeks were well tolerated; the rate of local adverse effects was similar to vehicle cream.

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